REMARKS/ARGUMENTS

Claims 44-46 and 49-51 are pending in this application. Applicants respectfully traverse the present rejections.

Claim Rejections – 35 U.S.C. §101/112, First Paragraph

Claims 44-46 and 49-51 are rejected under 35 U.S.C. §101 because, allegedly, "the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility."

Claims 44-46 and 49-51 are further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility, one skilled in the art clearly would not know how to use the claimed invention."

For the reasons outlined below, Applicants respectfully disagree.

The Legal Standard for Utility

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility".

Under the Utility Guidelines, an asserted utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a particular composition of matter is useful in general as a diagnostic tool, without also identifying the particular condition that is to be diagnosed using that diagnostic tool. However, when the condition that is capable of being diagnosed is specifically identified and linked to the claimed subject matter, the asserted utility satisfies the "specificity" requirement.

The requirement of a "substantial" utility defines a "real world" use, and derives from the U.S. Supreme Court's holding in Brenner v. Manson, 383 U.S. 519, 534 (1966) stating that: "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility."

In explaining the "substantial" utility standard, the Manual of Patent Examining Procedure (MPEP) § 2107.01 cautions, however, that Patent Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient" (MPEP § 2107.01, emphasis supplied). Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in MPEP § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility". (Emphasis supplied).

Moreover, the Utility Guidelines make clear that the requirement for the asserted utility be "substantial" arises solely for the purpose of excluding: "'throw-away' or 'insubstantial'.....utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. § 101". (66 Fed. Reg. 1092, 1098 (2001), emphasis supplied).

Finally, the Utility Guidelines also restate the Patent Office's long established position that any asserted utility must be "credible". "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (MPEP § 2107 II(B)(1)(ii)). According to the Revised Interim Utility Guidelines Training Materials published by the U.S. Patent Office in 1999, Office personnel must always accept a patent applicant's assertion of utility as "credible" unless (1) the logic underlying the assertion is "seriously flawed", or (ii) if the facts upon which the assertion of utility is based are "inconsistent with the logic underlying the assertion".

Moreover, the U.S. Patent Office also sets forth the evidentiary standard as to utility rejections under 35 U.S.C. § 101. In general, an Applicant's assertion of utility creates a presumption of utility that is sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement

of utility or its scope." In re Langer, 503 F.2d 1380, 1391 (CCPA 1974). See, also In re Jolles, 628 F.2d 1322 (CCPA 1980); In re Irons, 340 F.2d 974 (CCPA 1965); In re Sichert, 566 F.2d 1154, 1159 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956 (Fed. Cir. 1983) cert. denied, 469 U.S. 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Absolute predictability is not a requirement. Only after the Examiner makes a proper *prima facie* showing under this standard does the burden of rebuttal shift to the patent applicant.

Arguments:

Regarding the rejections based on Pennica and Konopka, Applicants submit that the teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene but not for *WISP-2 and WISP-3* genes. But, the fact that in the case of closely related molecules, there seemed to be no correlation between gene amplification and the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. As discussed above, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . " (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Accordingly, Applicants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between gene amplification and over-expression of mRNA or polypeptides in most genes, in general.

Similarly, in Konopka *et al.*, Applicants submit that the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of

bcr-abl mRNA produced from a single Ph^1 template." (See Konopka *et al.*, Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . . " is not sufficient to establish a *prima facie* case of lack of utility.

In conclusion, to establish a *prima facie* case of lack of utility, it is not enough to show that for one particular gene, a correlation does not exist. Rather, the law requires that the Examiner has to show evidence that it is more likely than not that such correlation, in general, does not exist. Such a showing has not been made, therefore, the Examiner has not made a sufficient case for a *prima facie* case of lack of utility and therefore, the Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial.

On the hand, Haynes *et al.*, as asserted before, showed that "there was a general trend, although no strong correlation between protein [expression] and transcript levels." (see Figure 1 and page 1863, paragraph 2.1, last line). When the proper legal standard is used, Haynes clearly supports the Applicants' position. This is all that's needed to meet the "more likely than not" evidentiary standard. Again, *accurate prediction* is not the utility standard.

The Examiner indicates that "the specification provides data showing a very small increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO232. There is no evidence regarding whether or not the PRO232 mRNA or polypeptide levels are also increased in these tumor samples".

Applicants strongly disagree. Applicants showed that the gene encoding for PRO232 was significantly amplified 2.056-fold to 5.28-fold, in five lung tumors or 2.00-fold to 5.32-fold in seven colon tumors (See Table 9). These values are considered significant based on a Declaration by Dr. Audrey Goddard submitted herewith. As Dr. Goddard states clearly on page 3 of her declaration:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a

gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the 2.00-fold to 5.32-fold amplification observed for PRO232 in the lung or colon tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration. Thus, barring evidence to the contrary, Applicants maintain that the fold amplification disclosed for the PRO232 gene is significant and forms the basis for the utility claimed herein.

Further, the Examiner seems concerned that data is provided "in a few tumor samples for PRO232". Applicants emphasize that they have shown significant DNA amplification in five lung tumors or in seven colon tumors samples in Table 9, Example 92 of the instant specification. The fact that 5 lung or seven colon tumors tested positive in this study does not make the gene amplification data, by any means, less significant or spurious. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers which do not give a positive hit for most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would certainly know that such tumor markers are very useful for better classification of tumors. Therefore, whether the PRO232 gene is amplified in five lung or seven colon tumors or in most lung or colon tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, whether the amplification data for PRO232 is considered significant is what lends support to its usefulness as a tumor marker.

Thus, the Examiner has not established a *prima facie* case for lack of utility. Rather, based on the significant gene amplification data observed for PRO232 in the lung or colon tumors, Applicants submit that PRO232 has patentable utility as a lung or colon tumor marker and further submit that this part of the utility rejection is improper.

Further, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed December 6, 2004) collectively teach that in general, gene

amplification increases mRNA expression. Applicants submit that these and numerous other articles show that generally, if a gene is amplified in cancer, it is more likely than not that the mRNA transcript will be expressed at an elevated level.

Applicants respectfully point out that in Orntoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Orntoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Orntoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Orntoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Orntoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Orntoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Orntoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers. The Examiner has stated that Applicants have not indicated whether PRO341 is in a gene cluster region of a chromosome. Applicants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters.

Applicants respectfully submit that the Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al.* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs was hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines was

hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also done on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

Further, Applicants respectfully submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels, the correlation between gene amplification and mRNA levels having already been established by the data shown in the Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* articles. Applicants further emphasize that the opinions expressed in the Polakis Declaration, including in the above quoted statement, are all based on factual findings. Regarding the non-acceptance of the Polakis declaration by the Examiner, Applicants draw the Examiner's attention to case law that clearly

establishes that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew (*In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985)). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument" (*In re Alton,* 37 USPQ2d 1578 (Fed. Cir 1966) at 1584 quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner" (*In re Alton, supra.*). Applicants further draw the Examiner's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered."

The statement in question from the Polakis Declaration that "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on his own experimental findings, which is clearly set forth in the Declaration. Accordingly, the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The Examiner further cites the Hu reference to show that "for genes displaying a 5-fold change or less in tumors compared to normal, there is no evidence of a correlation between altered gene expression and a known role in the disease." Applicants respectfully disagree.

Applicants respectfully submit that, contrary to the Examiner's assertion, the Hu *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO232 molecule, for the reasons outlined below.

The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining" (emphasis added). Therefore, as the title itself suggests, the conclusions in this reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to

provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in disease). The conclusions of Hu *et al.* however, only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column).

Moreover, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit. For instance, according to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). As is well known in the art, different statistical methods allow different variables to be manipulated to affect the resulting outcome. In this regard, the authors disclose that, "Initial attempts to search the literature" using the list of genes, gene names, gene symbols, and frequently used synonyms generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors add that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Hu *et al.* had to manipulate certain aspects of the input data, in order to generate, in their opinion, meaningful results. Further, because the frequency of citation for a given molecule and its relationship to disease only reflects the current research interest of a molecule, and not the true biological function of the molecule, as the authors themselves acknowledge, the "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). Therefore, based on these findings, the authors add, "[t]his may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). In other words, some molecules may have been underrepresented merely because they were less frequently cited or

studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions do not represent genes in general.

Therefore, Applicants submit that, based on the nature of the statistical analysis performed herein, and in particular, based on Hu's analysis of one class of genes, namely, the estrogen receptor (ER)-positive breast tumor genes, the conclusions drawn by the Examiner, namely that, "genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease (in general)" is not reliably supported.

Regarding the Ashkenazi declaration the Examiner says: "it has not demonstrated that the protein of the instant invention is differentially expressed in different tumors....the mere assertion that it may be differentially expressed does not provide a specific and substantial utility, and **is an invitation to experiment**" (emphasis added).

First of all, MPEP § 2107.01 cautions the Patent Office personnel to be careful not to interpret the phrase "immediate benefit to the public" or similar formulations, used in certain court decisions, to mean that, products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. In this instance, the Examiner has done just that and interpreted the "substantial utility" requirement to mean that "an asserted utility must exist in currently available form," which is legally incorrect. In fact, MPEP § 2107.01 adds that, "(r)ather, **any reasonable use** that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient" (emphasis supplied). Applicants have clearly demonstrated at least one "reasonable use" for the PRO232 polypeptide, that is, as a diagnostic marker for detecting or at least classifying lung or colon tumors. Such uses of the claimed invention serve a "practical purpose", which is not a "throw-away or insubstantial [use], such as the use of a complex invention as landfill." That is, Applicants have for the first time identified a particular human gene, the PRO232 gene, that is differentially amplified in certain types of cancerous human lung or colon tumors and this discovery provides for the first time, the ability to exploit this previously unknown, differential gene amplification pattern for the purpose of diagnosing or classifying lung or colon tumors of previously unknown pathology, which is not a "throw-away or insubstantial [use]."

Besides, the data disclosed in the instant specification are not preliminary. Based on the gene amplification data presented for the PRO232 gene in Example 92 of the specification, and the available art, there is ample support for the Applicants' position that increased gene amplification levels, more likely than not, predict increased mRNA and polypeptide levels. Thus, by providing a "reasonable use" for PRO232, Applicants respectfully submit that they have satisfied the "substantial utility" requirement for utility.

Further, the Examiner adds, " (o)verexpression of a gene produce in a cancer cell does not necessarily mean that the gene product is involved in cancer and that targeting the gene product would be therapeutic".

Again, Applicants respectfully submit that utility for PRO232 is based on data that supports its role as a tumor marker. The utility standard does not require proof that the gene product is "therapeutic". That would mean applying a heightened utility standard to this application.

Based on the above discussions, Applicants have demonstrated utility for the PRO232 polypeptide while the Examiner has not established a *prima facie* case for lack of utility. The data, for the reasons discussed above, clearly support a role of PRO232 as a lung or colon tumor marker. Further, since the present specification clearly teaches one skilled in the art "how to make and use" the claimed invention without undue experimentation, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

Priority

Applicants maintain that they rely on the gene amplification assay (Example 92) for patentable utility of the claimed polypeptide, PRO232. These results were first disclosed in U.S. Provisional Application 60/059121, filed September 17, 1997. From the discussions above, Applicants believe that the provisional application provides specific, credible and substantial utility for the claimed polypeptides in this invention. Thus, the present application is at least entitled to an effective filing date of **September 17, 1997**.

Claim Rejections – 35 U.S.C. §102(b)

Claims 44 and 46 remain rejected under 35 U.S.C. §102(b) as being anticipated by Rosenthal (dated 28 October, 1999).

As discussed above, the pending claims should be entitled to at least the effective filing date of September 17, 1997. The date of the cited primary reference is after the effective filing date of the present application. Hence, Rosenthal is not prior art under 102(b).
Hence Applicants request that this rejection be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-1618 P2C18**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Reg No. 43,626

Date: July 25, 2005

on behalf of Daphne Reddy

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